REMARKS

The Applicants note here that the Office Action dated April 10, 2007 in the subject application includes Rejections under 35U.S.C. §§ 112, 101 and 103 that are considerably similar, if not identical, to rejections made in parent application 09/364,425 which was issued as US Patent No. 6,653,086 ("the '086 patent"). The Applicants thus provide herein: 1) amended claims that conform to the structure of the claims of the '086 patent, and 2) arguments for the patentability of the claims that mirror those used to overcome these rejections during prosecution of the '086 patent. The Examiner is directed specifically to the response filed by Applicants on November 8, 2001 in the '086 patent, which was used as a template for the remarks below.

The Applicants have made every effort, both in drafting claim amendments and providing substantive remarks, to address each and every point in the current Office Action, relying on the successful outcome in the parent application as a template. Therefore, in view of the remarks set forth below, the Examiner is requested to allow Claims 1-3, 8-10, 20 and 21, the only claims pending and under examination in this application.

FORMAL MATTERS:

Claims 1-3, 8-10, 20 and 21 are pending after entry of the amendments set forth herein.

Claims 4-7 and 11-19 have been canceled without prejudice.

Claim 1 is amended to conform with the structure of the claims of the '086 patent. Support for these amendments can be found throughout the application as originally filed, e.g., on pages 25-29 and Example 8A starting on page 36 of the application as filed.

Claim 8 is amended to include SEQ ID NOs as requested by the Examiner.

Claims 20 and 21 have been added. Support for these claims can be found throughout the specification. For example, support for claim 20 can be found on page 18, lines 11-13; support for claim 20 is found in claim 8 as originally filed (which lists mammalian constitutively active G protein coupled orphan receptors) and the Examples.

As no new matter is added by way of these amendments, entry of the amendments by the Examiner is respectfully requested.

OBJECTIONS TO THE SPECIFICATION

The Examiner has objected to the specification because the priority information needs to be updated.

In response, Applicants have amended the priority claim in the specification to update the information as requested by the Examiner. Withdrawal of this objection is thus respectfully requested.

The Examiner has objected to the drawings because each Figure must be described separately in the brief description of the drawings.

In response, Applicants have amended the description of Figures 12 and 13 in the specification as requested by the Examiner. Withdrawal of this objection is thus respectfully requested.

SEQUENCE RULES COMPLIANCE

The Examiner asserts that the Application fails to comply with the sequence rules. Specifically, the Examiner states that the sequences in Figure 18 must be identified by their SEQ ID NOs and that the sequences referred to in Claims 8 and 13 require SEQ ID NO designations.

In response, the Applicants have amended the description of Figure 18A-L to specify the SEQ ID NOs of the sequences shown therein. The Applicants have also amended Claim 8 to include SEQ ID NOs as requested by the Examiner. Claim 13 has been canceled.

In view of the above, the Applicants submit that the application is in compliance with the sequence rules. Applicants further note that these changes conform to those made in the '086 patent.

REJECTIONS UNDER §112, ¶2

Claims 1-4 and 8-16 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

In making this rejection, The Examiner asserts that it is not clear what the terms "partial agonist", "inverse agonist" and "compound efficacy" mean. The Examiner further alleges that claims 1 and 12 are indefinite due to a perceived difference between the preamble of the claims and the claim steps.

Applicants provide below a copy of the claims of US Patent 6,653,086, the parent of the present application for the Examiner's convenience.

What is claimed is:

1. A method for identifying one or more compounds as an agonist or inverse agonist of an endogenous, constitutively active G protein coupled cell surface receptor, wherein the endogenous ligand for said receptor has not been identified, comprising the steps of:

(a) providing a GPCR Fusion Protein, said GPCR Fusion Protein comprising:

(i) an endogenous, constitutively active G protein coupled cell surface receptor, wherein the endogenous ligand for said receptor has not been identified; and

(ii) a Gsα protein;

(b) contacting said GPCR Fusion Protein with one or more candidate compounds;

(c) measuring the ability of said compound to inhibit or stimulate the activity of said receptor; and

(d) identifying one or more of said compounds to be agonist or inverse agonist of said receptor, wherein said compound is identified as an agonist by stimulating the activity of said receptor, and said inverse agonist is identified by inhibiting the activity of said receptor.

2. The method of claim **1**, wherein one or more of said compounds are directly identified as an inverse agonist to said receptor.

3. The method of claim **1**, wherein one or more of said compounds are directly identified as an agonist to said receptor.

* * * * *

Independent claim 1 of the subject application (as amended) reads as follows:

> 1. A method for directly identifying a candidate compound as an agonist or inverse agonist of an endogenous, constitutively active G protein coupled orphan receptor, comprising the steps of:
>
> (a) providing a GPCR Fusion Protein, said GPCR Fusion Protein comprising:
>
> (i) an endogenous, constitutively active G protein coupled orphan receptor; and
>
> (ii) a G protein; and
>
> (b) contacting said GPCR Fusion Protein with a candidate compound;
>
> (c) measuring the ability of said compound to inhibit or stimulate the activity of said receptor; and
>
> (d) identifying said compound as an agonist or an inverse agonist of said receptor, wherein said compound is identified as an agonist by stimulating the activity of said receptor, and said compound is identified as an inverse agonist by inhibiting the activity of said receptor.

As is clear from above, independent claim 1 of the subject application has been amended in a manner reflective of claim 1 of the allowed parent application (the '086 patent), which claim was deemed to meet the requirements of the second paragraph of 35 U.S.C. §112 by this Examiner.

With regard to the removal of the term "partial agonist", the Applicants note that the amendments to claim 1 does not narrow the scope of the claim or affect any potential range of equivalents, as the term "agonist" encompasses "partial agonists."

The Examiner asserts that "since the receptors used in the instant method are orphan receptors which do not have a defined or known universal intracellular response, it is not clear which parameters are measured to determine if a compound is an agonist, partial agonist or partial antagonists so as to allow the metes and bounds of the claim to be determined." (Office Action at page 5).

As argued during prosecution of the '086 patent, the Applicants respectfully direct the Examiner's attention to page 33, lines 1-12, of U.S. Patent Application Number 09/060,188 ("the '188 application"), the entire disclosure of which is incorporated by reference in the present application (see page 1 of the present application). Page 33, lines 1-12 of the '188 application state:

> A variety of second messenger screening assays can be employed to detect the receptor-mediated cellular response. The assay chosen primarily depends upon the type of receptor and the secondary pathway it activates. For example, for some G protein-coupled receptors an adenylyl cyclase activated system would provide the appropriate assay. For other G protein-coupled receptors, a phospholipase C linked assay would be appropriate. Appropriate assays for tyrosine kinase and other receptors are available and known to those skilled in the art. Preferred assays are summarized below. ***The assays of constitutively activated receptor activity not only demonstrate the functioning of the receptor activity, but they also provide a means to directly determine when the level of that activity has been decreased or increased. Thus, compounds which are inverse agonists would be expected to lower the observed basal level of activity while compounds which are agonists would be expected to increase the activity level above baseline.*** (emphasis added).

In addition, the instant specification describes several assays which can be utilized in connection with the claimed methods to determine whether a compound is an agonist or inverse agonist, e.g., [^{35}S]GTPγS assays (Specification, page 16) and cAMP detection assays (Specification, page 17). By way of example, the instant specification states that "[A]ssays that detect cAMP can be utilized to determine if a candidate compound is an inverse agonist to the receptor (i.e., such a compound which

contacts the receptor would decrease the levels of cAMP relative to the uncontacted receptor" (Specification, page 17).

From the specification, it is clear that a skilled artisan could readily compare the functional response of a constitutively activated GPCR contacted with a candidate compound versus the same constitutively activated GPCR contacted with a control (or "blank"). The difference in response between treatment with a compound and treatment with a blank determines whether the compound is an agonist or antagonist.

With regard to the term "compound efficacy", the Applicants maintain that it is clear and would be readily understood by a skilled artisan. For example, the specification specifically defines "compound efficacy" at page 9 to mean "a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed receptor binding affinity. A most preferred means of detecting compound efficacy is via measurement of GTP (via [^{35}S]-GTPγS) or c-AMP, as further discussed in the Example section of this patent document."

Nevertheless, solely to advance prosecution, Applicants have amended the claims to remove the term "compound efficacy", rendering the rejection, to the extent it refers to compound efficacy, moot.

With regard to the term "inverse agonists", the Applicants note that this term is found in claim 1 of the issued '086 patent. As argued during prosecution of the '086 patent, the term "inverse agonist" is defined in the instant specification at page 11 as: "materials (e.g., ligand, candidate compound) which bind to either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes." Moreover, those skilled in the art readily understand the instant usage of the term "inverse agonist". Indeed, the term "inverse agonist" is used in the Seifert et al. reference (J. Biol. Chem. 1998, Vol. 273, No. 9, 5109-5116), cited by the Examiner as alleged support for its rejection under 35 U.S.C. §103(a), discussed infra. (*See*, page 5114). Accordingly, Applicants respectfully submit that the term is clear and definite to those skilled in the art.

With respect to the perceived difference between the preamble of the claims and the claim steps, claim 1 has been amended to include an *identifying* step as suggested by the Examiner.

The Examiner asserts that claims 2-4, 15 and 16 are indefinite because it is unclear what directly identifies the compound as an inverse agonist, agonist or partial agonist. Claims 4, 15 and 16 have been cancelled herein, thus, the rejection now applies only to pending claims 2 and 3. Pending claims 2 and 3

parallel issued claims 2 and 3 in the '086 patent. Specifically, both pending and issued claims 2 and 3 recite direct identification of inverse agonist and agonists. Further, as stated above and in the response in the parent '086 patent case, the specification teaches assays for directly identifying inverse agonists and agonists of constitutively activated receptors (see discussion above of '188 application, page 33, lines 1-12).

Accordingly, the Applicants respectfully submit that claims 2 and 3, which mirror claims 2 and 3 of the issued '086 patent, are clear and definite.

Finally, the Examiner asserts that claims 8 and 13 are indefinite because SEQ ID NOs for the listed orphan receptors are missing. Applicants have amended claim 8 to insert SEQ ID NOs for the listed orphan receptors and claim 13 has been canceled. As such, Applicants submit that this aspect of the §112, second paragraph, rejection has been adequately addressed.

Claims 9, 10, 11, and 14 were rejected for depending upon allegedly indefinite base (or intermediate) claims. Claims 11 and 14 have been canceled. Applicants submit that the rejection of claims 9 and 10 has been adequately addressed in view of the amendments and remarks presented with respect to the base claims.

In view of the amendments to the claims (which conform to those of the '086 patent) and the foregoing arguments, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

REJECTIONS UNDER §101 AND §112, ¶ 1

Claims 1-4 and 8-16 were rejected under 35 U.S.C. §101 because the claimed invention is allegedly not supported by either a specific and substantial asserted utility or a well established utility.

In making this rejection, the Examiner presents arguments that are said to show that the asserted specific utility is not substantial. The Applicants note that the Examiner's arguments are nearly identical to those provided during prosecution of the '086 patent and which were overcome by Applicants.

As noted above, the Applicants have amended independent claim 1 in a manner similar to claim 1 of the '086 patent. This claim was deemed by the present Examiner to meet the requirements of the 35 U.S.C. §101. Therefore, the Applicants provide below a brief summary of the main arguments and evidence of record in the '086 patent regarding meeting the utility requirement, which the Examiner considered persuasive during its prosecution.

Summary of the Claimed Invention

Claims 1-3, 8-10, 20 and 21 are pending in this application. Claim 1, the only independent claim pending and under examination in the present application, is directed to a method of directly identifying compounds having agonist or inverse agonist activity to an endogenous, constitutively active G protein coupled orphan receptor comprising: providing a GPCR Fusion Protein, the Fusion Protein comprising an endogenous, constitutively active G protein-coupled receptor and a G protein; contacting the GPCR Fusion protein with a candidate compound; measuring the ability of the compound to inhibit or stimulate the activity of the receptor; and identifying the compound as an agonist or inverse agonist of the receptor, where the compound is identified as an agonist if it activates receptor activity and where the compound is identified as an inverse agonist if it inhibits receptor activity.

The Claims Provide a "Specific Utility"

The pending claims provide a specific utility. As recognized by the Examiner, the claimed methods can and are being used to directly identify lead compounds which affect receptor activity.

The Asserted Utility is Credible

According to Utility Examination Guidelines, a well established utility is a "specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art."

As noted above, Applicants submit that a specific utility has been established. Applicants further submit that a credible utility has also been provided: i.e., that the utility is "believable to a person of ordinary skill in the art based on the totality of the reasoning provided."

The claimed invention is directed to a method of using constitutively activated orphan receptors to directly identify candidate compounds (as inverse agonists or agonists) utilizing constitutively activated receptors. Because ligand dependent activated receptors have been used for discovering modulators of the receptor function, then ligand-independent activated receptors (i.e., constitutively activated receptors) can also be utilized, and have been utilized by Applicants, to discover compounds which act as inverse agonist or agonists of the receptor.

Therefore, Applicants' asserted utility cannot be questioned when all evidence and reasoning provided by the Specification is believable to a person of ordinary skill in the art.

The Claims Have Substantial Utility

The Examiner alleges that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

In brief, the Examiner asserts that: 1) because an orphan receptor does not have, by definition, a corresponding endogenous ligand that is known, neither the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on a specific disease state; and 2) constitutively activated orphan receptors likewise have no known function.

Based upon these two assertions, the Examiner further states that "...the corresponding asserted utilities are essentially methods of identifying lead compounds which affect constitutively activated orphan receptor activity, which does not define a 'real world' context of use... Since neither the specification nor the art of record disclose any activities or properties that would constitute a 'real world' context of use for the claimed method of identifying compounds having activity of inverse agonist or agonist activity, further experimentation is necessary to attribute a utility to constitutively activated orphan receptors and to the compounds that bind the constitutively activated orphan receptors." (Office Action, pages 10-11).

As described in detail during prosecution of the '086 patent, the functional role of an orphan receptor can be assessed and understood prior to identifying a receptor's endogenous ligand. This position was supported by third party publications (e.g., those skilled in the art have stated that tissue-specific expression of genes can provide clues to their role in pathology (Browne, M.J. 78 J. Biotechnology 247,248 (2000)) as well as a Declaration of Stanley J. Watson, M.D., Ph.D. (the Watson Declaration), one of skill in the art, which was filed in application U.S. serial number 09/060,188 and is attached hereto as Exhibit 1.

In brief, the third party references and the Watson Declaration makes clear that the functional role of an orphan receptor can be assessed and understood prior to identifying the receptor's endogenous ligand. Information that is relevant to revealing an orphan receptor's role include: where the receptor is expressed; the systems and circuits within which a receptor is located; how the receptor is expressed in normal versus disease state; and changes in receptor expression in response to certain conditions. This type of information can readily guide the skilled artisan to deduce the functional role of a receptor. Simply stated, drug discovery does not require the identification of a receptor's endogenous ligand as asserted by the Examiner.

Applicants respectfully note that the techniques employed in determining one or more functional role of a receptor are performed prior to applying the claimed invention. Upon determining a function of the receptor of interest, the claimed invention can be applied to the receptor target whereby an inverse agonist or agonist can be directly identified. This is a real world use for the claimed invention. That the

skilled artisan may decide to conduct additional studies using such compounds (e.g., medicinal chemistry to ascertain if more potent, cost-effective drugs can be developed) is not dispositive of the utility of the claimed invention.

By definition, inverse agonists and agonists are compounds that, upon contact with a receptor target, modulate the function of the receptor compared to the receptor's natural functional activity. These two classes of compounds acting on a constitutively activated receptor can be directly identified because they impact the receptor's normal downstream signaling system. As described in the specification and discussed in the Watson Declaration, because these downstream systems are based upon G proteins, one skilled in the art can understand the proteins modulated by an orphan GPCR (see, e.g., Watson Declaration at paragraph 18). Therefore, the candidate compounds identified by the claimed method are within a class of compounds that, by definition, act to change the function of a receptor's endogenous functional activity. Thus, the compounds identified do far more than merely "bind" to the receptor: rather, they affect the receptor's downstream functional activity.

In view of this, the Applicants submit that the claimed invention provides for a well-established utility. Indeed, the claimed invention allows functional analyses and drug discovery assays to be conducted with GPCRs even when the endogenous ligand has not yet been identified (i.e., orphan GPCRs).

Therefore, the Applicants submit that the claimed methods have a substantial utility in that the claimed methods are drawn to identifying agonist and inverse agonist compounds for such functionally characterized orphan GPCRs. Indeed, in Dr. Watson's opinion, it is both scientifically and factually incorrect to assert that constitutively activated orphan receptors have no known function. (See, Waston Declaration, paragraph 22(b)(l)).

In the absence of evidence to the contrary, the Applicants submit that the Watson Declaration alone requires a withdrawal of the rejection upon reconsideration.

Brenner v. Manson

As was done in the '086 patent, the Examiner cites *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966) as a basis for explaining the concept behind the phrase "real world" use for a claimed invention to comport with 35 U.S.C. §101. The Examiner makes reference to the view asserted by the Supreme Court in *Brenner v. Manson*:

> Congress intended that no patent be granted on a chemical compound whose "utility" consists of its potential role as an object of use testing[.] [A] patent is

> not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

The fact pattern of *Brenner v. Manson* was discussed in detail during prosecution of the '086 patent. In brief, Manson claimed a process for producing a compound but failed to provide an indication of any utility for the compound. Further, a reference cited for supporting a "well-established" utility did not focus on the compound made by the Manson process, but rather a class that included the compound. According to the reference, the disclosed class of compounds might prove to be useful in the role recited therein. This was not deemed sufficient support for utility. Thus, because Manson had no utility for the product made by the claimed process, the claimed process had no utility under §101.

The Applicants submit that *Brenner v. Manson* merely underscores the original Congressional intent behind the 1952 Patent Act regarding Section 101 - an applicant must disclose some identifiable benefit for the claimed invention in order to be patentable under §101. This position is supported in *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), in which the Federal Circuit, relying on *Brenner v. Manson* for support stated that:

> The threshold of utility is not high: An invention is useful under Section 101 if it is capable of providing some identifiable benefit. 51 USPQ2d at 1702.

Based on the above, the Applicants submit that these three words are dispositive to issues under §101: **Some. Identifiable. Benefit.** In essence, a long line of well-grounded case law has established that under §101, the disclosure need merely provide an indication of usefulness of the invention. The threshold is so low under §101 that it is only when a claimed invention is totally incapable of achieving a useful result or incapable of serving any beneficial end that a rejection can properly be applied, and sustained, under §101.

The Applicants submit that the subject application fully discloses **some identifiable benefit** for the claimed invention, and thus meets (and exceeds) the requirements under 35 U.S.C. §101. Indeed, the Applicants note that the claims of the present application (as amended) conform to those of the '086 patent, the issued parent of the present application.

Real World Use

In April of 2000, Arena pharmaceuticals, Inc. (the assignee of the subject application) announced a drug discovery alliance with Eli Lilly & Company, one of the world's leading pharmaceutical companies. Dr. August M. Watanabe, Executive Vice President, Science and Technology, for Eli Lilly,

stated in a press release issued in connection with the announcement of the collaboration that included technology covered by the claims pending in the application: "Arena has developed a very powerful platform for drug discovery that could substantially speed up the overall process for drug development." (Watanabe, A.M., M.D., Eli Lilly News Press Release, April 17, 2000, provided as Appendix A in the November 8, 2001 response in the '086 patent).

On May 29, 2000 Arena entered into a collaboration with Taisho Pharmaceutical Co., Ltd. This collaboration includes application of the technology covered by the pending claims to orphan GPCRs of interest to Taisho.

The Applicants submit that these collaborations provide further proof of the utility (or "real-world" value) of the claimed invention. Major pharmaceutical corporations do not invest millions of dollars in collaborations for technologies that have no "real world" use.

In view of the amendments to the claims and the arguments above, which mirror the amendments and arguments provided in the '086 patent, the Applicants submit that the claimed invention clearly fulfills the utility requirements under 35 U.S.C. §101. Withdrawal of this rejection is thus respectfully requested.

REJECTIONS UNDER §112, ¶1

Claims Rejected Under 35 U.S.C. §112, First Paragraph Claims 1-4 and 8-16 were rejected under 35 U.S.C. §112, first paragraph because the claimed invention is allegedly "not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Claims 1-4 and 8-16 were rejected under 35 U.S.C. §112, first paragraph solely because the claimed invention allegedly did not provide for a well-established utility nor a substantial utility. Because Applicants have established a well-established utility and a substantial utility that would constitute a real world use, one skilled in the art would clearly know how to use the claimed invention.

Therefore, Applicants respectfully request that this rejection also be withdrawn.

REJECTIONS UNDER §103(A)

Claims 1-4 and 8-16 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Seifert et al. (J. Biol. Chem. 1998, Vol. 273, No. 9, 5109-51 16) in view of Scheer et al. (J. of Receptor and Signal

Transduction Research, 1997, Vol. 17, 57-73) and further in view of Song et al. (Genomics, 1996, Vol. 28, 347-9), Bertin et al. (PNAS USA, 1994, Vol. 91, 8827-8831) and Wise et al. (J. Biol. Chem., 1997, Vol. 272, No. 39, 24673- 24678). Applicants respectfully traverse this rejection.

The Applicants note that this rejection is identical to the §103 rejection presented by the Examiner in the May 8, 2001, Office Action in the '086 patent. Due to the similarity of the claimed subject matter of the '086 patent and the subject application, the Applicants submit that the arguments that overcame this rejection in the '086 patent apply with equal force to the subject claimed invention. For the convenience of the Examiner, a brief summary of the arguments submitted in the '086 patent is provided below (see the response filed November 8, 2001 in the '086 patent).

To support a conclusion that the claimed combination is directed to obvious subject matter, either the references must expressly or implicitly suggest the claimed combination or the Examiner must present a convincing line of reasoning as to why the skilled artisan would have found the claimed invention obvious in light of the teachings of the references. Further, the Examiner is prohibited from basing an obviousness rejection on hindsight reconstruction by including knowledge "gleaned only from applicants disclosure . . ." In re McLaughlin, 170 USPQ 209,212 (CCPA 1971).

Deficiencies in Seifert, Scheer, Bertin, and Wise

Seifert is drawn to "Different Effects of Gsα Splice Variants on β2-Adrenoreceptor-mediated Signaling", and discusses the generation and testing of the β2-Adrenoreceptor coupled to splice variants of Gsα. The β2-Adrenoreceptor, although a G Protein Coupled-Receptor, is not an orphan G protein coupled cell surface receptor. Indeed, the endogenous ligand for the β2-Adrenoreceptor is known and the receptor has been characterized. As acknowledged by the Examiner, Seifert fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Also acknowledged by the Examiner is the fact that Seifert fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

Finally, Seifert fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, the Scheer reference discusses "[t]he activation process of the α_{1B}-adrenergic receptor: Potential role of protonation and hydrophobicity of a highly conserved aspartate." However, ligands for the β2-Adrenoreceptor are known (see, for example, Table 1 of Scheer which

discusses ligand binding properties of the adrenergic receptor), and the receptor has been characterized. Scheer fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Scheer also fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

Finally, Scheer fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, Bertin discusses the "[C]ellular signaling by an agonist-activated receptor/Gsα fusion protein", and discusses fusions of the β2-Adrenoreceptor/Gsα. As discussed in relation to the Seifert and Scheer references, ligands for the β2-Adrenoreceptor are known (see, page 8828 of Bertin which discusses the use of ICYP as a ligand), and the receptor has been characterized (see Table 1 and Figure 3 which set forth pharmacological properties of the receptor). Bertin fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

In addition, Bertin also fails to teach or even disclose the particular G protein coupled receptor for which the endogenous ligand has not been identified -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

Finally, Bertin also fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, the Wise reference discusses the "[R]ole of Functional Interactions between the α_{2a} -Adrenoreceptor and Acylation-resistant Forms of $G_{i1\alpha}$ by Expressing the Proteins from chimeric Open Reading Frames", and discusses fusions of α_{2a}-Adrenoreceptor and $G_{i1\alpha}$. However, ligands for the α_{2a} -Adrenoreceptor are known (see, page 24674 of Wise which discusses the use of RS-79948-197 as a ligand), and the α_{2a} -Adrenoreceptor has been characterized. Wise fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Further, Wise also fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR2 1, OGRI, GHSR, RE2 and AL022171.

Finally, Wise fails to teach or suggest the final candidate identification step recited in the claims as amended.

Therefore, the combined teachings of Seifert, Scheer, Bertin, and Wise fail to teach or even suggest at least the following: 1) a method for directly identifying a non-endogenous candidate

compound as an inverse agonist or an agonist, to an endogenous, constitutively active orphan GPCR, 2) particular orphan G protein coupled receptors (e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171), and 3) the final candidate identification step recited in the claims as amended.

Song fails to Remedy the Deficiencies in Seifert, Scheer, Bertin, and Wise

The Song reference fails to remedy the deficiencies of Seifert, Scheer, Bertin and Wise, alone or taken in combination. Song fails to teach or even suggest a method for directly identifying a non-endogenous candidate compound as an inverse agonist or an agonist, to an endogenous, constitutively active orphan G protein coupled cell surface receptor. As its title indicates, the Song reference discusses the "Molecular Cloning and Chromosomal Localization of Human Genes Encoding Three Closely Related G Protein-Coupled Receptors", one of which is GPR6, an orphan GPCR.

However, Song fails to teach or suggest any method for identifying agonists or inverse agonists of a GPCR, less still a method for identifying agonists or inverse agonists of a constitutively active orphan GPCR.

In addition, Song also fails to teach or suggest the final candidate identification step recited in the claims as amended.

Therefore, the applicants submit that the combined teachings of the cited references fail to teach or suggest each and every limitation of the claimed invention.

The Examiner also asserts that one would be motivated to modify the teachings of Seifert, Scheer, Bertin and Wise with the teaching of Song (described by the Examiner as a constitutively active GPCR), to allegedly achieve Applicants' claimed invention, citing several passages from the cited references as alleged motivation for modifying the teachings of the same.

However, none of the cited passages contains any disclosure or suggestion whatsoever to apply the disclosure of methods relating to GPCRs with known ligands to orphan GPCRs. Indeed, none of the quotations provided by the Examiner refer to orphan receptors at all, and Applicants are unable to locate any reference to orphan receptors in any of Seifert, Scheer, Bertin and Wise.

Further, the Song reference fails to teach or suggest any method for identifying agonists or inverse agonists of a GPCR. Thus, in addition to a lack of legally sufficient reason to combine the teachings of the cited art, even when so combined the combination would not teach Applicants' invention as presently claimed. Prior to Applicants' invention, there was no teaching in the art that constitutively active orphan G Protein-Coupled Receptors were useful for determining agonists and

inverse agonists of the receptor. Rather, prior research involving orphan GPCRs was focused on identifying the ligand of the receptor, often using homology to receptors with known ligands as a guide. The prevailing wisdom in the GPCR field was that the determination of agonists or antagonists of a GPCR was an activity that invariably happened after the ligand was identified.

Accordingly, the skilled artisan had no reason to combine the teachings of Seifert, Scheer, Bertin and Wise with the teachings of Song. Indeed, the only source of such motivation is Applicants' own disclosure, and, as has been invariably held by the Courts, the use of an Applicant's specification as reason to combine or modify references in an obviousness analysis is not permissible.

In view of the discussion above, it is clear that the Examiner has failed to establish a *prima facie* case of obviousness for the claimed invention. Indeed, this same rejection was successfully traversed by the Applicants in the '086 patent, which claims similar subject matter.

Therefore, because the Examiner has failed to provide a legally sufficient reason to combine the teachings of references as asserted in the Office Action, and because such combination would not result in Applicants' claimed invention, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-005CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: October 9, 2007

By: /David C. Scherer/ Reg. No. 56,993
David C. Scherer, Ph.D.
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Enclosure(s):

Exhibit 1: Copy of Watson Declaration

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